What is being claimed is not a DNA sequence but a polynucleotide encoding a specific protein, which protein is provided in the specification. The claims meet the requirements of §112 for this subject matter. All that §112 requires is that the specification enable a skilled person to make and to use the claimed polynucleotide. The specification provides sufficient teaching so that a skilled person would be able to obtain the polynucleotides as claimed. The specification provides ample guidance on obtaining the claimed polynucleotides, in particular example 8.

It is not necessary that the exact DNA sequences provided be used. The specification provides all the information necessary to obtain a polynucleotide as claimed. The claimed polynucleotides encode an insoluble protein with a molecular weight of 55 kD and which binds to TNF. The specification describes obtaining this protein encoded by the claimed polynucleotides, determining its molecular weight and properties, and obtaining the polynucleotides encoding the protein. This is all that is required. Thus any polynucleotides coding for the insoluble 55 kD TNF-binding protein as claimed are part of this invention.

§112 does not require that applicants exemplify all possible DNA sequences which fall under the claims. As shown above, the claims and specification are commensurate in scope, which is all that §112 requires. In reversing a rejection under 35 U.S.C. §112, the Court in In re Robins, 166 USPQ 552 (CCPA 1970) notes at page 555 that it is a misapprehension of the function of the disclosure to require that the disclosure support generic language in a claim by being equally broad in naming, and using representative compounds in examples.

> "If the examiner and/or the board intended a rejection under the first paragraph of Section 112, it must be reversed inasmuch as the specification contains a statement of appellant's invention, which is as broad as appellant's broadest claims, and inasmuch as the sufficiency of the specification...to enable one skilled in the art to practice appellant's process broadly as it is claimed has not been questioned... Mention of representative compounds encompassed by generic claim language

> clearly is not required by §112 or any other provision of the statute." (emphasis added)

The polynucleotides as claimed, encoding the insoluble 55 kD TNF-binding protein which fully described in the specification, can be obtained by a skilled person based on the disclosure. Even if many such polynucleotides were covered by the claims, examples of each such polynucleotide are not required, since the disclosure provides means for obtaining them as claimed. See also In re Borkowski, 164 USPQ 642 (CCPA 1970).

The use of the phrase "TNF binding protein" has also been rejected on the basis that this is unduly broad in describing any TNF-binding protein with a molecular weight of 55 kD.. As shown above, the specification examples provide in detail means for obtaining the claimed protein which binds TNF and has a molecular weight of 55 kD. Methods for determining the characteristic TNF binding and molecular weight are provided. All that §112 requires is that the claims be commensurate with the specification, whether the claims cover a single protein or whether multiple proteins could be covered. There is no need to exemplify each possible protein (see for example In re Robins and In re Borkowski, supra). Here, the specification teaches a 55 kD TNF binding protein and polynucleotides encoding the protein. This is all that is required under §112.

That experimentation could be required to determine whether a polynucleotide encodes an insoluble 55 kD TNF-binding protein and falls within the scope of the claims is not a basis for rejection under 35 U.S.C. §112. Attention is directed to Gore v. Garlock, 220 USPQ 303 (CAFC 1983), where the Court held that:

> "Assuming some experimentation were needed, a patent is not invalid because of a need for experimentation." (at 316)

In accordance with Gore, the specification provides means and guidance for determining that a protein is an insoluble TNF binding protein and has a molecular weight of 55 kD, and for

expressing a polynucleotide to determine that it encodes such a protein. This is fully consonant with §112. Even if a large amount of such experimentation were needed, a §112 rejection would not be proper. See for example In re Wands, 8 USPQ2d 1400 (CAFC 1988). The Court stated in reversing a §112 rejection based on undue experimentation:

> "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed." (at 547).

The specification provides more than a reasonable amount of guidance and direction for a skilled person to obtain and determine that a polynucleotide encodes an insoluble 55 kD TNF-binding protein using methods which are routine to a skilled person. There is no basis for rejection under 35 U.S.C. §112, first paragraph.

It is also alleged that the molecular weight is not sufficiently specific because measurements could vary by 10 kD. However there is no support for this allegation that it is not possible to determine a molecular weight of 55 kD. If the accuracy of any statement in the specification is doubted, it is necessary that more than an allegation be made, there must be a basis in evidence that it is not possible to determine a 55 kD protein (see for example In re Marzocchi, 169 USPQ 369, 370 (CCPA 1971). What is claimed is a polynucleotide encoding an insoluble 55 kD protein, not a 35 or 65 kD protein, and means for determining molecular weight are provided in the specification and further are well known in the art. is not a basis for rejection that the Examiner is not convinced that what is disclosed is a 55 kD protein.

Based on the foregoing, there is no basis under §112 to limit the claimed invention to the specific DNA sequences provided in the specification.

The Examiner has rejected the claim language "comprising" in the claims on the basis that anything could be added to either end of the claimed polynucleotide, and addition of certain entities might change the biological activity of the resulting polynucleotide. This is no basis for a §112 rejection. The claimed polynucleotides encode a TNF-binding protein. Any polynucleotide which does not encode such a protein is not a claimed polynucleotide. As shown above, the specification provides means for obtaining the claimed polynucleotides and ascertaining that they encode the 55 kD TNF-binding protein. As stated in overturning a §112 rejection in Ex parte Henderson, 176 USPQ 143 (POBA 1972), "The mere possibility that a composition may "comprise" besides its stated elements...other materials which could defeat the applicant's intention, does not necessarily make the description indefinite or extend it beyond the applicant's intention." Here, comprising does not extend the invention beyond the claimed polynucleotides encoding an insoluble 55 kD TNF binding protein. Any polynucleotide which does not so encode, is not part of the invention.

In order to encompass a polynucleotide as claimed encoding an insoluble 55 kD TNF-binding protein, it is not necessary to be able to predict whether or not an additional sequence will affect the properties of the protein so extensively that it ceases to have that activity and structure therefore is no longer the claimed polynucleotide. All that is necessary is that the specification provide the guidance necessary for a skilled person to obtain the claimed polynucleotide, which as demonstrated above, it does.

Based on the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 44-61 under 35 U.S.C. §112, first paragraph. It is also submitted that there is no basis for a §112 rejection of new claims 62-65 for the same reasons.

35 U.S.C. §102 rejection

Claim 51 has been rejected under §102 as anticipated by Capon (WO 89/02922). Claim 51 has been amended and is now directed to a polynucleotide which hybridizes to the entire DNA sequence encoding the fusion protein of claim 48, under conditions in which a DNA sequence having one or more deletions, substitutions, or additions from that DNA sequence would hybridize to the DNA sequence of claim 48. It is alleged that, as previously claimed, such a polynucleotide would hybridize to the DNA disclosed by Capon, because Capon discloses DNA encoding a fusion protein which has immunoglobulin sequences in common with the immunoglobulin sequences of the protein encoded by the claimed polynucleotide. As amended, there is no further issue as to this reference. Capon does not disclose TNF binding proteins, even less does Capon disclose a polynucleotide encoding a fusion protein comprising a TNF-binding protein. Thus, the Capon polynucleotide would not hybridize to the entirety of a polynucleotide encoding a protein binds to TNF, since the Capon polynucleotide does not encode any TNF binding sequences for such hybridization. In addition, hybridization would not occur under conditions in which only a fairly homologous polynucleotide with minor variations would hybridize. This is what is intended to be covered by the claim, and to clarify this the language "a DNA sequence having one or more deletions, substitutions, or additions from that DNA sequence" has been added from the specification. It is respectfully requested that the rejection under §102 be withdrawn.

35 U.S.C. §103 rejections

Claims 48-55 and 58-61 have been rejected under §103 over Wallach (EP 308 378) in view of Capon. This rejection is respectfully traversed.

The invention of claims 48-55 is a polynucleotide made up of a subsequence encoding an insoluble 55 kD TNF binding protein or its soluble TNF-binding fragment, and a subsequence

encoding all but the first domain of a human immunoglobulin heavy chain constant region (claims 58-61 are directed to corresponding vectors and hosts). It is alleged that Wallach discloses the insoluble 55 kD TNF binding protein and a corresponding polynucleotide. There is no disclosure or suggestion in Wallach of a fusion protein, and Capon is cited to provide immunoglobulin fusion proteins. Capon does not disclose or suggest such proteins fused with the TNF binding proteins, even less the insoluble 55 kD TNF binding protein. Capon is also cited to provide a method for obtaining a corresponding gene based on a protein.

It is considered obvious to substitute the protein allegedly disclosed by Wallach into a Capon fusion construct, and to obtain the corresponding polynucleotide. However, Wallach does not disclose a 55 kD TNF binding protein. Nor is there any suggestion in either reference to combine immunoglobulin sequences to encode a fusion protein with any TNF binding protein, much less the insoluble 55 kD protein of this invention

Wallach does not disclose or provide any means for obtaining an insoluble 55 kD TNF binding protein encoded by the claimed polynucleotide. The patent law requires an enabling disclosure for a valid §103 rejection (In re Hoeksma, 158 USPQ 597 (CCPA 1968)). However, there is no enabling disclosure of the claimed 55 kD protein in the present case. Thus, there can be no basis for this §103 rejection.

The protein encoded by the claimed polynucleotide has a molecular weight of 55 kD on SDS-PAGE after HPLC. The Wallach protein has an entirely different molecular weight of 26-28 kD on SDS-PAGE after HPLC (see Wallach, page 3 lines 50-51 and page 7 line 44 through page 8 line 5). Wallach discloses that an intermediate preparation in the purification procedure contains material having a molecular weight in the range of 40-80 kD. This is not the molecular weight of the purified Wallach protein, it is only a purification intermediate. As stated by Wallach

> "The TNF Inhibitory Protein of the invention may be found in human urine. When crude preparations thereof derived from human urine concentrate were chromatographed on Ultrogel ACA 44 gel filtration column, it showed an apparent molecular weight of 40-80 Kda. The substantially purified protein, which is substantially free of proteinaceous impurities, has a molecular weight of about 26-28 Kda..."(page 3 lines 46-50, emphasis added)

As this demonstrates, the preliminary and impure preparation of Wallach has fractions in the molecular weight range of 40-80 kD. However the Wallach protein is a different protein having a molecular weight of 26-28 kD.

Wallach does not disclose an insoluble protein which binds TNF or a polynucleotide encoding such a protein. The claimed protein is insoluble. However Wallach discloses only a soluble protein. The Wallach protein is a soluble protein capable of being isolated from urine because of its solubility. In contrast, the claimed protein is insoluble - it is isolated from cell membranes. Wallach discloses no such proteins obtained from cell membranes, and does not anticipate an insoluble protein as claimed. The claimed protein and the Wallach protein go through different preliminary purification steps, because the Wallach protein is soluble and isolated from urine and the claimed protein is insoluble and isolated from cell membranes. However, both proteins reach their final phase of purification after HPLC and SDS-PAGE, and are clearly different proteins when purified, having different molecular weights

Wallach does not provide fragments of the protein encoded by the claimed polynucleotide. Applicants have shown that the claimed protein and the Wallach protein are different proteins. When proteins are different, there is no reason to suppose that one is a fragment of the other unless the art provides a disclosure supporting such an assertion. No such support is provided. Thus Wallach would have to disclose to one skilled in the art that the Wallach protein is a fragment of an insoluble 55 kD protein, and Wallach provides no such disclosure. Not only is there no 55 kD protein disclosed, but the Wallach soluble 26-28 kD protein is not taught to be a fragment of any

protein of any molecular weight. Therefore, Wallach does not suggest that the Wallach protein is a fragment of a 55 kD protein. There is nothing in Wallach to suggest identity of these two different proteins other than that the Wallach protein is allegedly also capable of binding TNF, having a similar activity to the claimed protein. In the absence of an insoluble 55 kD TNF-binding protein, there is no suggestion of a polynucleotide encoding such a protein.

As demonstrated above Wallach does not provide a polynucleotide encoding an insoluble 55 kD TNF binding protein. Capon does not disclose any fusion proteins made from 55 kD TNF-binding proteins. In the absence of art disclosing such a protein and corresponding polynucleotide, there can be no basis for this rejection of the claimed polynucleotide encoding a 55 kD TNF binding protein. Accordingly, even if Capon disclosed a means by which polynucleotides may be obtained from corresponding proteins, as alleged, this is no basis for rejection because there is no insoluble 55 kD TNF-binding protein made available in the cited art, even less a fusion protein which contains such a protein.

Further, even if a polynucleotide encoding an insoluble 55kD TNF binding protein were available in the art, there is no suggestion of a polynucleotide encoding a fusion protein with such a TNF-binding protein and immunoglobulin heavy chain sequences as claimed. Capon is cited to provide polynucleotides encoding fusion proteins. However, Capon does not disclose fusion proteins in general. Capon discloses specific fusion proteins made up of immunoglobulin heavy chain sequences combined with a sequences from a protein which is closely related to immunoglobulins, i.e. CD4. The Capon fusion partners are explicitly limited to not highly polymorphic members of the immunoglobulin superfamily (page 6 lines 18-21).

It is well settled that in order to combine references, there must be some teaching or suggestion in the references supporting the combination. (In re Fine, 5 USPQ2d 1596, 1598 (CAFC 1988). There is no such teaching or suggestion here. The only reference disclosing fusion proteins

is Capon, which must therefore be the relied on to provide suggestion to combine. But Capon does not suggest making polynucleotides encoding an active fusion protein by combining protein fragments from protein families unrelated to any proteins disclosed in Capon. Capon does not suggest making fusion proteins with any proteins other than immunoglobulins or relatives of immunoglobulins such as CD4. Even less does Capon suggest a fusion protein using a 55 kD TNF-binding protein which is nowhere disclosed. Therefore, Capon does not suggest the claimed polynucleotide encoding a fusion protein combining immunoglobulin sequences with the completely unrelated 55 kD TNF binding protein.

Based on the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 48-55 and 59-61 under 35 U.S.C. §103 over Wallach in view Capon.

Claims 44-47 and 56-57 have been rejected under §103 over Stauber (JBC 263:19098) in view of Lee (Science 239:1288) or Wozney (Meth. Enzymol. 182:738) This rejection is respectfully traversed.

The claimed invention is a purified, isolated polynucleotide which encodes a 55 kD insoluble protein which binds human tumor necrosis factor (TNF), and vectors and host cells containing the polynucleotide. None of the references provide such a polynucleotide.

Stauber is cited to disclose a purified, homogenous TNF binding protein, and does not disclose polynucleotides. Lee and Wozney are cited to disclose methods of obtaining a polynucleotide from a purified protein with a known amino acid sequence. Neither Lee or Wozney disclose a TNF-binding protein.

Both Lee and Wozney teach that it is necessary to have a purified homogenous protein in order to obtain its gene (see Wozney, title "Using a Purified Protein to Clone its Gene, and Lee page 1289, column 2 paragraph 2). However no such purified protein is available, even less an insoluble 55 kD TNF-binding protein.

Stauber does not disclose a homogenous protein. The TNF receptor preparation of Figure 6 demonstrates Stauber's highest level of purification (after immunoaffinity chromatography and SDS-PAGE), but is not a homogenous preparation. The silver-stained gel in Figure 6 shows a mixture of different bands, and not a homogenous protein. Thus Stauber's most purified preparation does not provide homogenous protein with a molecular weight of 55 kD.

According to Stauber, the gel of Figure 6 corresponds to a 165,000-fold purification of TNF receptor. This does not mean that the preparation is homogenous, it means that the preparation is 165,000 purer in TNF receptor than the starting material, a cell lysate. The gel of Figure 6 contains multiple bands. This itself demonstrates that Stauber does not have a homogenous preparation, no matter what the extent of purification. In addition, Stauber himself states that his 165,000-fold purification corresponds to only 20% purity, which does not approach homogeneity. Further, whatever the purification, this preparation does not even represent the TNF receptor itself. What is purified is a complex of TNF receptor covalently linked to TNF-a.

> "The combined purification by both immunoaffinity chromatography and preparative SDS-PAGE was approximately 165,000-fold. The overall yield for these two steps was estimated to be about 34 ng of receptor from approximately 1.5 x 10^{10} U937 cells based on the content of ^{125}I labelled TNF-a in the product. The cross-linked receptor is approximately 20% pure at this point." (page 1903, column 1, paragraph 2).

The Stauber reference does not disclose a homogenous 55 kD TNF binding protein. The reference itself states that it is an impure preparation. Therefore, Stauber does not provide basis for a homogenous protein, even less a polynucleotide or any means for obtaining a polynucleotide.

It is alleged that Lee provides a method for obtaining a purified protein on page 1289, column 2, paragraph 2. However, Lee does not teach any means to purify. All Lee does is disclose that urate oxidase was purified to homogeneity in order to be sequenced in order to provide probes. This does not disclose purification of urate oxidase. It does teach the necessity of a purified homogenous protein to obtain corresponding DNA. Even if Lee disclosed purification of urate oxidase, this does not suggest that a TNF-binding protein would be successfully purified by the same method. The purification method depends on an individual protein. A method successful with one protein does not teach purification of another unrelated protein.

There is no teaching in the cited references of a polynucleotide encoding a 55 kD TNF-binding protein, nor is there any means disclosed of obtaining such a polynucleotide. There is no basis for a §103 rejection.

In addition, even if the references did provide a method by which a polynucleotide could be obtained, this would not provide sufficient basis for a §103 rejection.

Applicants have claimed a polynucleotide, not a method of isolating a polynucleotide. That a compound may be prepared by known methods and materials does not make that compound obvious. Disclosure of compounds such a proteins which are not genes but provide information by which genes may be isolated and disclosure of methods for using such compounds to isolate genes, do not make obvious specific genes.

In In re Deuel, 34 USPQ2d 1210 (CAFC 1995), a claimed polynucleotide was rejected based on the combination of a reference providing the proteins encoded by the polynucleotide, with a reference disclosing how to obtain polynucleotides from proteins. The Board of Appeals upheld this rejection. In reversing the Board, the CAFC stated that it was improper to reject the claimed polynucleotide "based on the alleged obviousness of a method of making the molecules." (at 1214). The CAFC further stated that although

> "...the general idea of the claimed molecules, their function, and their general chemical nature may have been obvious from Bohlen's teaching, and the knowledge that some gene existed may have been clear, the precise DNA molecules of claims 5 and 7 would not have been obvious over the Boolean reference, because Boolean teaches proteins, not the claimed or closely related Dna molecules. ...The PTO's theory that one might have been motivated to try what Deuel in fact accomplished amounts to speculation and impermissible hindsight reconstruction of the claimed invention. ... A general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search." (at 1215)

Similarly, in In re Bell, 26 USPQ2d 1529, the CAFC reversed the Board's §103 rejection of polynucleotides based on a reference disclosing the complete amino acid sequences proteins encoded by the claimed polynucleotides and a reference disclosing a method for isolating polynucleotides by making probes corresponding to known amino acid sequences. As stated by the CAFC:

> "Finally, the PTO emphasizes the similarities between the method by which Bell made the claimed sequences and the method taught by Weissman. The PTO's focus on Bell's method is misplaced. Bell does not claim a method. Bell claims compositions, and the issue is the obviousness of the claimed compositions, not of the method by which they are made (citations omitted)." (at 1532)

In Bell and Deuel, the CAFC held that just because it is possible to translate a known amino acid sequence into a Dna probe and use that probe by known methods to isolate a claimed polynucleotide, this does not make it obvious to do so under §103. In the subject case, just because it may be possible to the amino acid sequence of the 55 kD TNF binding protein and use this

sequence to ultimately obtain a polynucleotide, is no basis for rejection. At best, this rises to the level of obvious to try, which is not a permissible standard. Furthermore, not even the purified protein is available, even less the amino acid sequence. As stated above in Deuel, " [a] general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search." This is particularly true of the present case, since the disclosed technical information is more distant from the claimed polynucleotide than in Bell and Deuel. In these cases the amino acid sequences specifically corresponding to the claimed polynucleotide were available. Here, no such sequences are available. A §103 rejection is misplaced.

Based on the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 44-47 and 56-57 under 35 U.S.C. §103 over Stauber in view of Lee or Wozney.

Applicants respectfully solicit allowance of the subject application.

Respectfully submitted,

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